

Spaceflight Nutrition Research: Platforms and Analogs

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INTRODUCTION

Understanding human adaptation to weightlessness requires research in either the true microgravity environment or in a ground-based model. Over the years, many flight platforms have been available, and many ground models have emerged for both human and animal studies of the effects of spaceflight on physiology. In this review, we provide a brief description of these models and the main points to be considered when choosing a model. We do not intend to provide a comprehensive overview of each platform or model, but rather to provide the reader with an overview of the options available for space nutrition research, and the relative merits and/or drawbacks of each.

SPACEFLIGHT

Space nutrition research has been conducted to some extent with crew members on virtually every mission ever flown. It may have included only basic monitoring of medical parameters, or merely consisted of testing before and after the mission, without inflight data collection.

Studies that require only pre- and postflight data collection are not very different from other research with human subjects, as the facilities and equipment required for studying the crew can typically be made readily available. However, postflight studies, when used as an alternative to inflight studies, must be interpreted carefully. The reentry process is physically demanding and crews are typically fatigued, potentially confounding early postflight data collection. This is not an issue when readaptation of the system being studied is slow, as with

bone mass. In studies of these systems, data need not be obtained immediately after landing. For systems that recover more rapidly (such as fluid balance, and endocrine and humoral factors), postflight data collection may not provide the same quantitative or qualitative results as an on-orbit study.

When a study requires on-orbit data collection, extra constraints are imposed. The very process of training a second party to conduct (and be a subject in) an experiment is unusual for most scientists. Severe constraints on electrical power requirements, stowage (volume and weight), and conditioned stowage (volume and weight to be stored in freezers or refrigerators) are placed on experimental equipment. These constraints are further compounded by the ability of equipment to function in a microgravity environment. Moreover, potential environmental impact and containment of any potential hazards must be taken into account. These hazards include toxic vapors that may be released by the experimental equipment, or the materials used for equipment construction that may offgas during flight (often these vapors are at very low levels, but in a closed spacecraft, they may accumulate). Flammability, toxicity, heat, electromagnetic radiation, and vibration transfer can also affect suitability for flight.

Many aspects of weightlessness are often not considered in the initial planning of an experiment. Even the most basic issues are difficult to overcome. How does one determine body mass of a weightless subject or collect a urine sample without the aid of gravity? These basic issues are crucial to the success of spaceflight experiments, and often make the larger issues even more daunting.

Current Platforms

Two active space platforms are now deployed: the International Space Station (ISS) and the Space Shuttle. The International Space Station (Fig. 1), as the name suggests, is a multinational effort to establish an orbiting base for research. The first element was launched from Russia in 1998, and the first crew took up residence in November 2000. In October of 2002, the sixth crew of 3 will arrive on orbit. The process of building the ISS will take several more years, and with budget issues reshaping the final plans, the station's final form and crew complement is still somewhat speculative.

Current research opportunities on the ISS are extremely limited because of resource constraints, specifically lack of crew time (for training and for experiment operations on orbit), power limitations, and frozen stowage limitations. Perhaps one could imagine that doing research on the ISS now is like trying to do it in a laboratory that is under construction, where the construction workers are also intended to serve as both scientists and research subjects.

Nonetheless, at completion, the station is intended to house a crew of 7 multinational astronauts, within a vehicle with a pressurized volume equivalent to that of two 747 airliners. Laboratory facilities will include a full complement of hardware for collecting, processing, and storing biological samples. Animal facilities will provide the ability to harvest tissues and samples during extended-duration missions.

For over 20 years the Space Shuttle has provided a valuable platform for short-term research projects, with missions typically lasting 1 to 3 weeks. Because volume of the crew compartment is limited (it is very small compared to the overall size of the Shuttle), modules are often flown in the payload bay to accommodate research hardware. The two modules used most

often are the Spacelab and the Spacehab (Fig. 2). The science hardware for each Shuttle flight is determined by the specific experiments to be performed on that flight. Several dedicated life sciences missions have been conducted, including studies of the effects of spaceflight on a variety of physiological systems.

Animal housing is also available on the Shuttle when required to meet the goals of the mission. Mice and rats, in addition to a variety of less highly developed animal forms such as fish and bees, have been flown on the Shuttle on several occasions. In rare cases, on-orbit euthanization has been possible. Establishing ground-based controls for these studies has been challenging, and attempts have been made to simulate the vibration, noise, and stress of launch and reentry, which clearly can alter physiological responses as much as weightlessness itself.

Earlier Platforms

The Russian Mir Space Station (Fig. 3) provided a valuable research base from 1986 through 2001. The multiple-module station housed research equipment to support many disciplines, including exercise and cardiovascular experiments. During the joint US-Russian research programs of the mid- to late 1990s, additional life sciences research equipment was flown. From a biochemist's point of view, a significant resource of the NASA-Mir program was the ability of the Shuttle to provide for conditioned (refrigerated or frozen) storage of materials being brought to the Mir station, and of samples collected on Mir to be returned to Earth on the Shuttle. This was critical for the success of many experiments, as the launch/return vehicle from the Mir, the Soyuz, has a very limited capacity for this type of stowage.

America's first space station, Skylab, provided a life sciences laboratory for 3 crewed missions in 1973 and 1974. Extensive metabolic balance studies were conducted, with complete dietary intake monitoring and complete urine and fecal collections. Without advanced technology to reduce the time, inconvenience, and resources required for these types of collections, we will likely never again see such complete metabolic studies performed during spaceflight. For comparison: on the 84-d Skylab IV mission, crew members collected their urine for 84 days, whereas the crewmember on Mir with the most frequent sampling collected only 12 days of urine samples during a 4-month mission.

Very limited inflight data collection was performed in many earlier space programs, including the Vostok-Voskhod, Mercury, Gemini, Apollo, Soyuz, and Salyut programs. Although some nutrition issues (including the most basic question: can one swallow in weightlessness?) were addressed in these programs, the majority of relevant nutrition science has come from the later programs.

GROUND-BASED MODELS — HUMAN STUDIES

Several ground-based analogs of weightlessness have been developed, with many variant forms. As always, the selection of a particular model depends on the specific research question(s) to be addressed, the resources and facilities available, as well as other factors. Our intent here is to briefly describe several of the models, and to point out key positive or negative aspects. For detailed discussion of the value of a model for any given system, we defer to the individual articles in this issue.

Bed Rest

Bed rest is a common analog for simulating weightlessness, with the value of the model changing as a function of the physiological system of interest. Depending on the system to be studied, duration of bed rest can vary from hours to months. For some studies, horizontal bed rest is appropriate, whereas investigators attempting to simulate the fluid shift of weightlessness use a -6° (or sometimes greater) head-down tilt. Regardless of specific design variables, bed rest studies are extremely complex, difficult, and time-consuming for all parties involved.

Subject selection and screening are important to minimize (or eliminate) preexisting confounding factors. Identifying subjects willing and able to participate in extended-duration bed rest studies is an art in itself, and ensuring compliance with all experiment constraints (including remaining in bed) requires vigilant monitoring. Prolonged bed rest may produce side effects and discomforts similar to those experienced during spaceflight, including headache, back pain, constipation, nasal congestion, and leg cramping. Investigators must determine, either before or (worst case) during the study, whether subjects will be allowed to take medicines as required to alleviate these symptoms, as these may impact the physiological systems under study.

Investigators must also define any exceptions to remaining in bed, such as allowing subjects to use a bedside commode for defecation rather than a bedpan. Subjects are usually allowed to lean on one elbow to eat their meals. Most facilities capable of supporting bed rest studies have horizontal shower facilities, although some investigators allow subjects a 5- to 10-minute break from bed rest for showers.

Dietary intake is an important issue for bed rest studies. The fact that energy expenditure decreases during bed rest, and thus maintenance of body mass requires reduction of food intake,

must be taken into account when controlling intake of specific nutrients. Although this is usually easy to accommodate, depending on the nutrient being studied, it can affect a researcher's ability to achieve constant total intake and a constant percent of the diet for the nutrient.

Even food provision during bed rest studies can be challenging. Some researchers have thought it essential to order same-lot food items to eliminate concerns about changes in nutrient intake through the duration of long-term or crossover design studies. This is scientifically ideal, but it can affect the budget for the experiment. Preventing subject boredom with menu cycles can also prove to be a difficult task.

As with any research protocol, there is no "right" or "wrong" bed rest design. At a minimum, the design should not compromise the system(s) being studied. Perhaps most important, the details of the protocol should be carefully reported in publications to allow better interpretation of between-study differences.

Immersion

Immersion is another means of simulating weightlessness. The two major variations are wet immersion and dry immersion. Wet immersion is conducted in a pool, with subjects dressed in water-resistant suits and submerged up to their necks in water. Dry immersion is a more advanced technique. It is also performed in a water pool, but the surface of the pool is covered with an excessive amount of water-resistant material (analogous to the surface of a water bed). The density of water creates a pressure gradient between submerged and floating parts of the body. Immersion can be an appropriate model for many systems. It produces many effects of

disuse that are similar to those of bed rest. It also simulates loss of body proprioception that occurs in microgravity. Many of the difficulties with bed rest studies also apply to the immersion models.

Single-Limb Immobilization

Single-limb immobilization has been used instead of bed rest primarily for musculoskeletal studies. Briefly, the subjects wear a device that prevents a limb from bearing weight, and they use crutches for locomotion. These studies allow within-subject comparisons with the contralateral leg as a control. Subjects may be free-living, making this model less resource-intensive than a bed rest study, however, the inability to monitor compliance may be an adverse consequence with such studies.

Isolation and Stress

Stress and isolation are likely contributors to the physiological effects of spaceflight (such as muscle loss and immune system changes) and to psychological issues of flight. Ground-based models of stress and isolation are thus sought to distinguish their effects from those of other aspects of spaceflight, such as microgravity. Many such paradigms exist, including submarine deployment, polar station research, sports competition, academic examinations, military training, and the occupational stresses seen in emergency services (such as law enforcement, medical services, and firefighting).

Confinement is one of the major stress factors in long-term spaceflight. It has cognitive components (the psychological discomfort of confinement) as well as noncognitive components (such as increased microbial contamination resulting from hygienic restrictions). Accordingly, confinement is widely used to simulate space station life in terrestrial environments. Several models of isolation have been studied, including Antarctic winter-over crews, submarine crews, and inmates.

To study interactions of the neurological, psychological, and immune system effects of stress, the academic exam is a well-established model. Moreover, it is a real-life complex stressor that includes cumulative effects of the chronic stress of preparation for the exam, the acute stress of taking an exam, and the tension of awaiting the results. These stressors can detrimentally alter the performance of many students each year, and increased illness among students under the stress of examinations is well documented.

One drawback to these models is that they typically incorporate additional stress factors that are not related to spaceflight, while producing discrete physiological alterations in subjects. Perhaps a better model to simulate spaceflight-like confined conditions is a specially designed chamber in which life-support systems, crew size, crew quarters, and other conditions are similar to those on a spacecraft (Fig 4). Several such chamber studies have been conducted in space agency facilities around the world. These space simulation chamber studies strive to simulate conditions of space missions ranging from several-day Shuttle flights to extended space station or planetary base missions. These analogs come as close as possible to mimicking temperature, humidity, noise, work/rest cycle, nutrition, hygiene, and communications onboard a spacecraft.

Parabolic Flight

For studies in which very short periods of weightlessness can induce measurable changes, parabolic flight is an option. NASA investigators use the KC-135 aircraft, which during a typical flight performs 40 parabolas, each with a period of weightlessness of about 25 to 30 seconds followed by about a minute of 1.5 to 1.9 g exposure. While the KC-135 is typically used for hardware and performance assessments, it is also used for scientific studies. Many cardiovascular and pulmonary studies in humans have been completed on this aircraft, and the KC-135 may even be used for *in vitro* cellular studies where chemical treatments can halt the specific processes being studied.

System-Unique Models

The utility of several models is limited to one or two physiological systems. The high-altitude environment may be used to study hematological changes, and centrifugation may be used to study aspects of the neurovestibular system. Patients with spinal cord injury may also be recruited into studies of skeletal muscle and bone loss.

GROUND-BASED MODELS—ANIMAL STUDIES

Rats are the subjects in the most commonly used ground-based animal models of spaceflight. These models are hindlimb suspension, limb immobilization, and limb casting. They are primarily used for studies of bone remodeling and skeletal muscle function. Hindlimb suspension, or unloading, is accomplished by placing a rodent in a body sling or suspending it by its tail. Within 2 weeks, the mass and strength of these animals' bone and muscle change significantly. An alternate method, hindlimb paralysis, can be accomplished by severing the caudal spinal cord or sciatic nerve. Hindlimb casting is also effective, but is used less often with rats than the other methods mentioned. Other animal models published in the literature, but used less often, include immobilization of a single limb of canines, disarticulation of the ulna of turkeys, and induction of estrogen deficiency in rats. Nevertheless, of the aforementioned ground-based animal models used to simulate some of the effects of microgravity, the one most universally used is the rat hindlimb suspension model.

GROUND-BASED MODELS—CELLULAR STUDIES

Certain cell culture systems can also be used as models for investigating altered gravity effects at the cellular level. Although there is some question whether other ground-based paradigms truly model microgravity, the High Aspect Ratio Vessel (HARV) and the Slow Turning Lateral Vessel (STLV) are effective models as they provide a randomized gravity vector and low shear stresses. The HARV (Fig 5) is a self-contained horizontally rotating cell culture system that allows diffusion of oxygen and carbon dioxide across a semipermeable membrane.

The HARV has a very low shear stress (0.5 dynes/cm^2) for 1- or 2-mm cellular aggregates. It has a time-averaged gravity vector of 10^{-2} g ; while that of near-earth free-fall orbit is 10^{-4} to 10^{-6} g . The STLV is similar to the HARV, but it is oxygenated by a center core membrane oxygenator and is intended for microcarrier cell culture and explant tissue cultures. As the STLV generally has a greater shear force than does the HARV, the latter is more often used as a spaceflight analog for cell cultures. Indeed, the HARV is a useful paradigm for studying cellular physiology in a ground-based cell culture system that has low shear stress and models microgravity.

CONCLUSION

Understanding the effects of spaceflight on the human body will enable humans to keep meeting the challenges of space exploration. Countermeasure development and testing will be required to ensure the health and safety of astronauts on short (days or weeks), long (months), and exploration (years) missions. The research needed to attain these goals is extensive, and will require ground-based and spaceflight studies, human and model system studies, and scientific expertise from investigator teams in virtually all disciplines. Selecting a model system is perhaps the most critical decision an investigator makes in designing an experiment, and understanding the benefits and limitations of the model is essential for incorporating specific findings into the overall framework of knowledge.

Figure Legends

Figure 1. The International Space Station (ISS) as seen from the Shuttle during a flight in late 2001. Assembly will continue over the next several years, with modules, support structures, and solar panels being added.

Figure 2. The Space Shuttle Endeavor with the SpaceHab in payload bay, as seen from the space station.

Figure 3. The Russian Mir space station, as seen from the Shuttle Atlantis during its departure after the final docking mission in 1998.

Figure 4. Closed environment chambers like this one are used to simulate closed environments and to test environmental and physiological adaptation to enclosed environments. This chamber, located in Houston at the NASA Johnson Space Center was most recently used for a series of tests known as the "Lunar/Mars Life Support Test Project," 30-, 60-, and 91-d studies of environmental (i.e., air and water) recycling systems, and supplemental studies of physiological effects of confinement on the 4-person crews.

Figure 5. The High Aspect Ratio Vessel (HARV).